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Claude F. Purchase, Jr.
Warner-Lambert Company LLC
2800 Plymouth Road
Ann Arbor, MI 48105

EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,174	ROARK, WILLIAM HOWARD	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 15, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Jan 29, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

This application claims benefit of provisional application 60/396910, filed 07/17/2002. Claims 1-9 are pending in this application and examined on the merits herein.

Claim Rejections – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claims concern a combination comprising valdecoxib and an additional compound defined as an allosteric inhibitor of matrix metalloprotease 13 having certain steric and hydrogen bonding characteristics. The compound is recited solely as a pharmacophore without defining the actual molecule that the Applicant wishes to claim. Absent any conventional structural information, Cartesian coordinates are not sufficient to allow one of ordinary skill in the art to determine what is being claimed. Specifically, molecules are described very poorly by Cartesian coordinates. A molecule's geometry is determined by:

A) Covalent and noncovalent bonds between individual atoms within the molecule,

B) Isomerization among rapidly intraconverting isomers

C) Rotational angles about freely rotating sigma bonds.

Of these three factors, only A) can be expected to remain constant over significant periods of time. Thus the vast majority of molecules do not possess a single, unique Cartesian geometry by which they can be clearly identified. The set of molecules accurately described by the Cartesian coordinates given in the claims is expected to shift over a period of microseconds, thus rendering identification of individual molecules which fit this description impossible. Furthermore, as the conformation of a molecule depends very strongly on its environment, the applicability of the claims to a particular pharmaceutical composition would depend on such factors as solvent, inactive binders, and crystal structure, as many compounds would have a structure fitting the claim language when in one solvent or crystalline form but not in another. In some cases, an organic acid or base would fit the Cartesian coordinates when in free acid or base form, and not fit the coordinates when in the form of the salt, even though the biological effects and pharmaceutical use of the two different forms are identical. Furthermore, the Applicant fails to specify whether the Cartesian coordinates given are meant to apply to the allosteric MMP-13 inhibitor when in the form of a solid, liquid, or solution before administration, when in solution under physiological conditions after administration to the subject, when bound to the molecular target, or all three of the above. In addition, since the 3-dimensional structures of organic molecules are difficult to predict, many compounds' structures can only be determined by synthesizing a sample of the compound in order to determine the structure by methods such as NMR spectroscopy or x-ray crystallography. For these reasons, organic compounds are

conventionally described not by Cartesian coordinates but by Lewis structures indicating only the connectivity between atomic nuclei and not distinguishing between separate conformational isomers of the same compound.

While it is noted that the specification contains numerous examples of individual molecules which allegedly are capable of fitting the stated coordinates when in particular conformations, such examples are given with the explicit instruction that they are not to be considered to in any way limit the scope of the claimed invention. Furthermore, said examples are listed either as conventional Lewis structures or by chemical name, rather than using the Cartesian notation found in the claims, thus failing to identify which examples fall under claims 2 and 3 and which fall only under claim 1.

Thus claims 2-3 fail to clearly and distinctly identify the subject matter to which they are directed.

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, the Applicant claims, "A combination, comprising valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof," as well as, "A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering to the mammal a therapeutically effective amount of a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof," as well as various dependant claims.

The specification as originally filed does not provide adequate support for the generic claims herein. In particular, the specification does not adequately convey to one skilled in the relevant art the precise definition of the category, "allosteric inhibitors of MMP-13". Said class of inhibitors is described in purely functional terms which do not adequately describe the invention to anyone who does not already know the scope of compounds which are allosteric inhibitors of MMP-13. Because the language of the claims is open-ended and contains no relevant structural information, the examples provided on pp. 63-149 are only an insignificant fraction of the total number of allosteric inhibitors of MMP-13 included by the claims. In fact, no listing of examples would adequately describe the claimed invention unless accompanied by a clear disclosure proving that said examples were exhaustive, or at least fully representative of the totality of all allosteric inhibitors of MMP-13. As an exhaustive knowledge of exactly which compounds are or are not allosteric inhibitors of matrix metalloprotease 13 is not

part of the ordinary skill in the biochemical or pharmaceutical art, this functional description is not adequate to fully describe the claimed invention.

Additionally, claims 2-3 recite sets of Cartesian coordinates which allegedly limit the scope of the claims. However, these coordinates are indefinite for reasons listed above and cannot be used by one skilled in the art to meaningfully define the scope of the claimed invention.

Functional language at the point of novelty, as herein employed by the Applicant, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate." The CAFC further clearly states that, "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405 (emphasis added), and that "It does not define any structural feature from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphasis added).

Moreover, the court of *In re Curtis* held that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability ... of any other species." (emphasis added, see *In re Curtis* 354 F.3d 1347,

69 USPQ2d 1274, Fed. Cir. 2004). The court of *Noelle v. Lederman* also pointed out that a generic claim to anti-CD40CR MABs lacked written description support because there was no description of anti-human or other species MABs, and no description of human CD40CR antigen. The court further pointed out that attempts to "define an unknown by its binding affinity to another unknown" failed. See 355 F.3d 1343, 69 USPQ2d 1508, Fed. Cir. 2004.

In the instant case, the claimed combination is deemed not to be adequately described. Thus, ordinary artisans could not predict the operability or lack thereof of any other species of chemical substance that is "an allosteric inhibitor of MMP-13".

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that the Applicant was in full possession of the invention as it is now claimed.

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain combinations of valdecoxib and with an allosteric matrix metalloprotease 13 inhibitor, does not reasonably provide enablement for combinations involving every possible allosteric MMP-13 inhibitor. This is a purely functional distinction or functional language. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to reliably determine the scope of the molecules claimed, absent undue experimentation.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The invention deals with a combination comprising valdecoxib and an allosteric inhibitor of MMP-13, and a therapeutic method for using said combination. The nature of the MMP-13 inhibitor is identified by functional, rather than structural language.

The state of the prior art: MMP-13 inhibitors are known to exist and are seen as useful drug candidates for the treatment of many diseases. None are actually in use as treatments for cartilage damage, arthritis, or pain. Most of the existing inhibitors are hydroxamate active site inhibitors which act by coordinating to the active site zinc, and are thus not allosteric inhibitors such as those involved in the claimed invention.

The relative skill of those in the art: The level of skill in the art is high, with a typical practitioner holding a Ph. D. or equivalent advanced degree in a an appropriate field.

The predictability or unpredictability of the art: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. It is important to note that the actual usefulness of a drug is affected by additional factors besides the activity of the drug against its molecular target in vitro. In particular, the claimed invention requires the compound to be biostable and bioavailable, as well as being nontoxic to the subject. These critical pharmacological properties cannot be predicted from *in vitro* inhibitory activity and a significant number of compounds which display excellent activity in the assay are expected to be poor drug candidates for this reason, and not useful in the methods of claims 5-9.

The breadth of the claims: There are no significant structural limitations on the MMP-13 inhibitor of the claimed invention. Every molecule that happens to have allosteric MMP-13 inhibiting activity is included as a possible component in the claims. Technically, inorganic acids, bases, and salts can be referred to as "allosteric inhibitors of MMP-13" as sufficient concentrations of acid, base, or salt will cause structural changes which inactivate the enzyme. While Cartesian coordinates are given for certain functional groups in claims 2-3, these are indefinite as described earlier, and thus useless in ascertaining the scope of molecules claimed. It is also noted that since there are no further limits on the physical, chemical, or structural characteristics of the claimed compounds, the claims include both organic and inorganic compounds, including such molecular entities as proteins, antibodies, nucleotides, polysaccharides, nanoparticles,

and possibly even viruses, provided that they possess allosteric MMP-13 inhibitory activity.

The amount of direction or guidance presented: The specification includes a description of several experimental protocols by which molecules included in the claimed invention may be identified. The molecular target of the invention is described as well. One skilled in the art wishing to practice the invention with a compound other than those explicitly disclosed would, based on the specification, be able to design a program of drug discovery to identify novel compounds which would be useful in the claimed therapeutic method. Additionally, references are cited that contain synthetic instructions for the synthesis of those allosteric MMP-13 inhibitors specifically given as examples in the specification. However, no instructions are given for synthesizing those claimed molecules not specifically mentioned as examples.

The presence or absence of working examples: The specification includes a lengthy recitation of individual molecules known by the Applicant to possess allosteric MMP-13 inhibitory activity. In all, there are 85 pages of examples, with roughly 10 examples per page on average. Said molecules have apparently been tested using at least one of the assays mentioned, but no experimental results, such as IC_{50} values, are listed. Thus one skilled in the art, in order to practice the invention, would have to repeat said experiments in order to determine which of the recited compounds possess stronger or weaker inhibitory activity. None of the recited compounds have been tested *in vivo*, as indicated by the absence of experimental data and the purely speculative language in the experimental protocols. Furthermore, none of the working examples are proteins,

antibodies, nucleotides, polysaccharides, nanoparticles, viruses, or any one of the other molecular entities besides organic small molecules that are included within the claim language.

The quantity of experimentation necessary: According to the Chemical Abstracts Service 2006 catalog, the Chemical Abstracts Registry contains entries for approximately 26 million organic and inorganic substances, all of which are potentially involved in the claimed method if they happen to possess allosteric MMP-13 inhibitory activity. The Sigma-Aldrich Rare Chemical Library contains over 80000 compounds, all of which are commercially available and also potential candidates for use in the claimed invention. The total number of compounds known either (a) to be allosteric MMP-13 inhibitors or (b) to not be allosteric MMP-13 inhibitors is merely an insignificant fraction of the total number of compounds whose allosteric MMP-13 inhibitory activity or lack thereof is not known. The existing literature does not identify any general method by which allosteric inhibitors of MMP-13 can be identified across all classes of molecular entities claimed other than by synthesizing and testing each one, and by the Applicant's own admission (specification, p. 3, line 22-p. 4, line 16) the inhibitors of the current invention are substantially different from the prior art and not significantly related in their mechanism of action to known MMP-13 inhibitors to make a comparison to the prior art useful for predicting the activity of the claimed compositions. In order to practice the invention with the full range of allosteric MMP-13 inhibitors beyond the limited number disclosed in the specification, one skilled in the art would be required to undertake a full-scale, high-throughput drug discovery program to discover the additional allsoteric

MMP-13 inhibitors not specifically recited in the specification. In fact, one would also be forced to retest even those molecules specifically identified in the specification, as no specific IC50 values are given by which one could determine which of the recited compounds are the best drug candidates.

In the process of screening the extensive number of compounds required to practice the claimed invention, one would be forced to synthesize said molecules. As no synthetic procedures are described and no references cited that teach synthetic protocols to synthesize allosteric MMP-13 inhibitors, or potential MMP-13 inhibitors, other than the admittedly incomplete list of examples, one wishing to practice the invention would be forced to design novel synthetic pathways. Since synthesis of organic small molecules is complex, the entire scope of claimed molecules cannot be synthesized by simple variations on a core synthetic scheme. In fact, current knowledge of the field of organic synthesis is far from complete, as evidenced by the fact that many synthetic schemes are still considered to be sufficiently novel to be patented, as evidenced by US patents 6500954, 6500955, and 6500972, all of which relate to synthetic methods. Since no structural limitations are given to the claimed invention, the list of compounds to be synthesized would include an enormously diverse set of structures and require an equally diverse array of synthetic procedures to produce them. Thus one of skill in the art would be forced to invest a considerable amount of time and effort devising chemical syntheses spanning all fields of organic, inorganic, and biological chemistry.

In addition to synthesizing candidate compounds and carrying out *in vitro* studies on the molecular target, one wishing to practice the therapeutic method of claims 5-9 would also be required to undertake *in vivo* tests in animal models of inflammation, arthritis, and pain, such as the ones disclosed in the specification. Animal experiments include, along with the actual surgery, administration of the potential pharmaceutical compound, and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated thousands of times, and involve the maintenance, killing, and disposal of at tens of thousands of experimental animals at minimum, to establish the suitability or lack thereof for each compound found to possess the desired activity *in vitro*.

The sort of industrial-scale interdisciplinary drug discovery program described in the preceding paragraphs would present an undue amount of experimentation to require of anyone wishing to practice the invention.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the unpredictability of the art, the broad scope of the claim, the relative lack of working examples, and the undue experimentation required, Applicants fail to provide information sufficient to practice the claimed invention for each and every combination of valdecoxib with an "allosteric inhibitor of MMP-13".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldman et. al. (PTO-1449 Reference Included by applicant) in view of Montana et. al. (PTO-1449 Reference Included by Applicant), van der Berg (PTO-894 reference included by examiner), and Smith et. al. (PTO-892 Reference included by Examiner)

Goldman et. al. teaches that Valdecoxib is, "A COX-2 Inhibitor for Treatment of Osteoarthritis, Rheumatoid Arthritis, and Primary Dysmenorrhea". (P. 1, title) Goldman et. al. does not teach the combination of Valdecoxib with an allosteric MMP-13 inhibitor or a method of using such a composition in the treatment of any diseases or disorders.

Smith et. al. teaches that doxycycline, a member of the tetracycline family of antibiotics, has the additional effect of inhibiting matrix metalloproteases, including

MMP-13. (P. 1142, figure 2) Smith et. al. additionally teaches that the observed inhibition is noncompetitive. (p. 1144, left column, under Kinetics of Inhibition and Figure 3) The authors therefore draw the conclusion that, unlike most MMP-13 inhibitors, doxycycline exerts its inhibitory activity at an allosteric site rather than by directly binding to the active site zinc. (p. 1144, third paragraph, p. 1145, first paragraph) These results demonstrate that doxycycline is, in the language of the instant claims, "an allosteric inhibitor of MMP-13".

Van der Berg teaches that MMP-13 is known to be involved in osteoarthritis and other kinds of cartilage injury (p. 453, first three paragraphs under the heading, "enzyme involvement") According to the reference, increased MMP-13 expression leads to osteoarthritis in mice, and increased levels of MMP-13 have been observed in other animal models of osteoarthritis.

Montana et. al. teaches that in conditions such as rheumatoid arthritis, "the natural balance of MMPs and TIMPs [tissue inhibitors of metalloproteases] is disrupted and the result is uncontrolled matrix degradation leading to cartilage, bone , and joint degradation." (p. 353, introduction)

Therefore, it would have been obvious at the time of the invention to combine the teaching of Goldman et. al. with the teachings of the preceding references by mixing valdecoxib with doxcycline to produce a pharmaceutical combination according to claims 1-4, and using said combination in a therapeutic method to treat painful inflammatory conditions, such as osteoarthritis, that are associated with excessive MMP-13 activity according to claims 5-9.

One of ordinary skill in the art would have been motivated to combine the teachings of the two references in order to treat diseases, such as osteoarthritis, that are caused by unbalanced MMP activity, while simultaneously treating the pain and inflammation caused by such conditions. One of ordinary skill in the art would have reasonably expected that because both drugs had already been independently validated against their relative molecular targets, and both were independently known to be useful for treating the same conditions (osteoarthritis and rheumatoid arthritis), combining the two would produce additive therapeutic effects in treating said conditions.

It has been held that it is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Therefore the invention taken as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 10/619777. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-10 of application No. 10/619777 include only subject matter which falls within the scope of the instant claims.

Claims 1-5 of said copending application claim a combination comprising valdecoxib and an allosteric alkyne inhibitor of MMP-13 having a structure falling within certain structural limitations. As instant claims 1-4 claim combinations of valdecoxib with all allosteric inhibitors of MMP-13 regardless of structure, said copending claims fall entirely within the scope of instant claims 1-4.

Copending claim 5 claims, "A pharmaceutical composition, comprising a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, with an allosteric alkyne inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. As the instant claim 4 claims combinations of valdecoxib with all possible allosteric inhibitors of MMP-13,

including allosteric alkyne inhibitors, said copending claim falls entirely within the scope of instant claim 4.

Copending claim 6 claims, "A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering to the mammal a therapeutically effective amount of a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13, or an pharmaceutically acceptable salt thereof." This claim is identical to instant claim 5 with the additional limitation that the allosteric MMP-13 inhibitor must be an alkyne, and thus falls entirely within the scope of instant claim 5. Copending claims 7-10 depend from copending claim 6 and introduce identical limitations to those introduced by instant claims 6-9, and are therefore entirely included within the scope of instant claims 6-9.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 10/619662. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-10 of application No. 10/619662 include only subject matter which falls within the scope of the instant claims.

Claims 1-5 of said copending application claim a combination comprising valdecoxib and an allosteric carboxylic inhibitor of MMP-13 having a structure falling

within certain structural limitations. As instant claims 1-4 claim combinations of valdecoxib with all allosteric inhibitors of MMP-13 regardless of structure, said copending claims fall entirely within the scope of instant claims 1-4.

Copending claim 5 claims, "A pharmaceutical composition, comprising a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, with an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. As the instant claim 4 claims combinations of valdecoxib with all possible allosteric inhibitors of MMP-13, including allosteric carboxylic inhibitors, said copending claim falls entirely within the scope of instant claim 4.

Copending claim 6 claims, "A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering to the mammal a therapeutically effective amount of a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric carboxylic inhibitor of MMP-13, or an pharmaceutically acceptable salt thereof." This claim is identical to instant claim 5 with the additional limitation that the allosteric MMP-13 inhibitor must be carboxylic, and thus falls entirely within the scope of instant claim 5. Copending claims 7-10 depend from copending claim 6 and introduce identical limitations to those introduced by instant claims 6-9, and are therefore entirely included within the scope of instant claims 6-9.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 10/619663 in view of Goldman et. al. (PTO-1449 Reference Included by applicant).

Claims 1-9 of copending application 10/619663 claim combinations of a cox-2 inhibitor other than celecoxib or valdecoxib with an allosteric inhibitor of MMP-13, as well as a pharmaceutical composition and method of treatment involving said composition. The language used exactly parallels that of instant claims 1-9 with the exception that the cox-2 inhibitor involved is not valdecoxib. Claims 1-9 of copending application 10/619663 do not claim combinations comprising valdecoxib or any pharmaceutical composition or therapeutic method involving such combinations. The specification of said copending application does not provide any reasoning by which valdecoxib alone among all COX-2 inhibitors is unsuitable for combination with an allosteric inhibitor of MMP-13.

Goldman et. al. teaches that Valdecoxib is, "A COX-2 Inhibitor for Treatment of Osteoarthritis, Rheumatoid Arthritis, and Primary Dysmenorrhea". (P. 1, title) Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of application 10/619663 by using valdecoxib as the COX-2 inhibitor in the claimed combinations, compositions, and therapeutic methods instead of using a COX-2 inhibitor other than celecoxib or valdecoxib.

One of ordinary skill in the art would have been motivated to combine the teachings of the two references in order to treat diseases, such as osteoarthritis, that

are caused by unbalanced MMP activity, while simultaneously treating the pain and inflammation caused by such conditions. One of ordinary skill in the art would have reasonably expected success because application 10/619663 already teaches a combination of a COX-2 inhibitor and an allosteric MMP-13 inhibitor, and because valdecoxib was already known to be a therapeutically effective COX-2 inhibitor for the treatment of arthritis and related conditions.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed in this invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Eric Olson
Patent Examiner
AU 1623
4/11/06

Anna Jiang
Supervisory Patent Examiner
AU 1623